

weight based on the total weight of the liposome.

Common to all four rejections is U.S. patent 5,716,638 to Touitou and indeed this reference is discussed at length in item 2 of the Official Action. Claims 1-14 and 16-17 stand rejected under 35 USC §103(a) as being unpatentable over Touitou (5,716,638) by itself or in combination Cauwenbergh (5,476,853).

It is counsel's understanding that the examiner's position is essentially as follows (taken from item 2, pages 2-3 of the current Official Action).

"Touitou discloses a method of preparation of liposomes containing lipophilic active agents, which includes terpenes. The method involves adding the lipophilic drug and Phospholipon in ethanol-propylene glycol either at room temperature or at 60 to 70 degrees, adding to distilled water and TEA (triethanolamine) and cooling the mixture []. (The) instant method differs from Touitou in the following way. In (the) instant method the terpenoid is dispersed in polyol (propylene glycol) at 60-70 degrees to which TEA is added and then (a) phospholipid solution in ethanol is added. To this mixture, water is then added. In Touitou, the lipophilic drug, phospholipid are added together in ethanol-propylene glycol mixture to which the TEA and water is added. Since the function of the base is to elevate the pH of a dispersion to alkaline values and since the addition of water to the phospholipid in the organic solvent in both Touitou and (the) instant method, it would have been obvious to one of ordinary skill in the art at the time the invention was made to vary the steps in the method of Touitou and still expect the formation of the liposomes. Touitou also differs from instant method in the last step; that is, the addition of the acid to change the alkaline pH of the liposomal suspension. However, since the preparations of Touitou are meant for the topical application of skin, it would have been obvious to one of ordinary skill in the art to change the alkaline pH resulting from the addition of TEA in Touitou to neutral or near neutral pH by the addition of an acid since these pH levels are compatible with skin. One of ordinary skill in the art would be motivated to change the alkaline pH of Touitou to pH of 5 to 7.5 since the reference to Cauwenbergh while disclosing liposomal skin formulations such as toilet waters and skin milk teaches that the final pH of 5 to 7.5 is preferable and this pH can be obtained by the addition of either a base or an acid or buffer such as citric acid or phosphoric acid or acetate buffer."

Considering then procedures claimed by applicant used to prepare their triterpenoid-containing liposomes pH regulation is a key factor.

Regarding pH regulation

Regulating pH by using a base and then using acid in the present invention is to prepare liposome containing a triterpenoid at a high concentration. This is totally different from regulating the pH of the cosmetic composition containing liposome merely in order to be compatible with skin.

More specifically, the object of the present invention is to provide liposomes containing a triterpenoid at high concentration while using a non-toxic solvent without intensive mechanical treatment. In order to incorporate triterpenoid at a high concentration uniformly into a liposome, the present invention employs triterpenoid having acid group, and by adding a base, the triterpenoid is transformed into its salt having surface activity. The transformed triterpenoid salt acts as a surfactant of high HLB, and it forms a mixed micelle system when mixed with a low HLB lipid. Then, the above-obtained mixed micelle system maintains its pH in a range of 10~11. By adding an acid to decrease its pH to 5~8, the triterpenoid salt transforms back to the original form having an acid group, and thereby loses its surface activity. This results in changing the mixed micelle system into a liposome. During the transformation, triterpenoid is loaded into the liposome at high concentration. (see column 2, third paragraph of specification of the present invention.) In other words, regulating pH by using a base and then using acid in the present invention is to prepare liposome containing triterpenoid at high concentration.

However, Cauwenbergh discloses that the final pH of 5~7.5 of a skin formulation is preferable and this pH can be obtained by the addition of either a base or an acid or buffer. Cauwenbergh discloses pH regulation of a skin formulation containing liposomes merely in order to be compatible with skin, not pH regulation in the preparation of liposome as in the present invention.

Regarding use of Triethanolamine (TEA)

Touitou merely discloses the use of TEA in the example of a gel preparation, but it does not disclose the reason why TEA is added to the gel preparation. In addition, Touitou does not disclose or suggest the combined use of base and triterpenoid of the present invention, i.e., to transform triterpenoid having acid moiety into its salt having surface activity so as to form mixed micelle system with low HLB lipid.

Further, Touitou does not disclose or suggest the use of acid to transform the triterpenoid salt back into its original form having an acid group, resulting in changing the mixed micelle system into a liposome, whereby triterpenoid is loaded into the liposome at high concentration.

In addition, the use of TEA in Delrieu is to prevent aggregation of liposomes, i.e., to stabilize the liposomes already prepared, which is different from that of the present invention which is to prepare liposome triterpenoid at high concentration.

The deficiencies in the rejection advanced in item 2 of the Official Action continue through the three additional obviousness rejections in items 3-5 and it is not believed to be necessary to discuss these in great detail as substantially the same issues namely pH regulation and the use of TEA are included in these three separate rejections.

It is noted that six references in item 4 and 7 references in item 5 have been asserted as the basis of the Examiner's third and fourth obviousness rejections. As the courts have stated, the fact that it is necessary to cite such a large number of references is, in and of itself, indicative of non-obviousness. *Minneapolis-Honeywell Regulator Company v. Midwestern Instruments, Inc.*, 298 F.2d 36, 38, 131 U.S.P.Q. 402, 403 (7th Cir. 1961); *The Ric-Wil Company v. E.B. Kaiser Company*, 179 F.2d 401, 404, 84 U.S.P.Q. 121, 124 (7th Cir. 1950); *Reynolds et al v. Whitin Machine Works*, 167 F.2d 78, 83, 76 U.S.P.Q. 551, 555 (4th Cir. 1948); and *Racal-Vadic, Inc. v. Universal Data Systems*, 1980 U.S. Dist. LEXIS 15864, *81, 207 U.S.P.Q. 902, 927 (N.D. Ala. 1980).

For the above reasons it is respectfully submitted that the claims of this application define inventive subject matter. Reconsideration and allowance are solicited. Should the examiner require further information, please contact the undersigned.

Respectfully submitted,

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